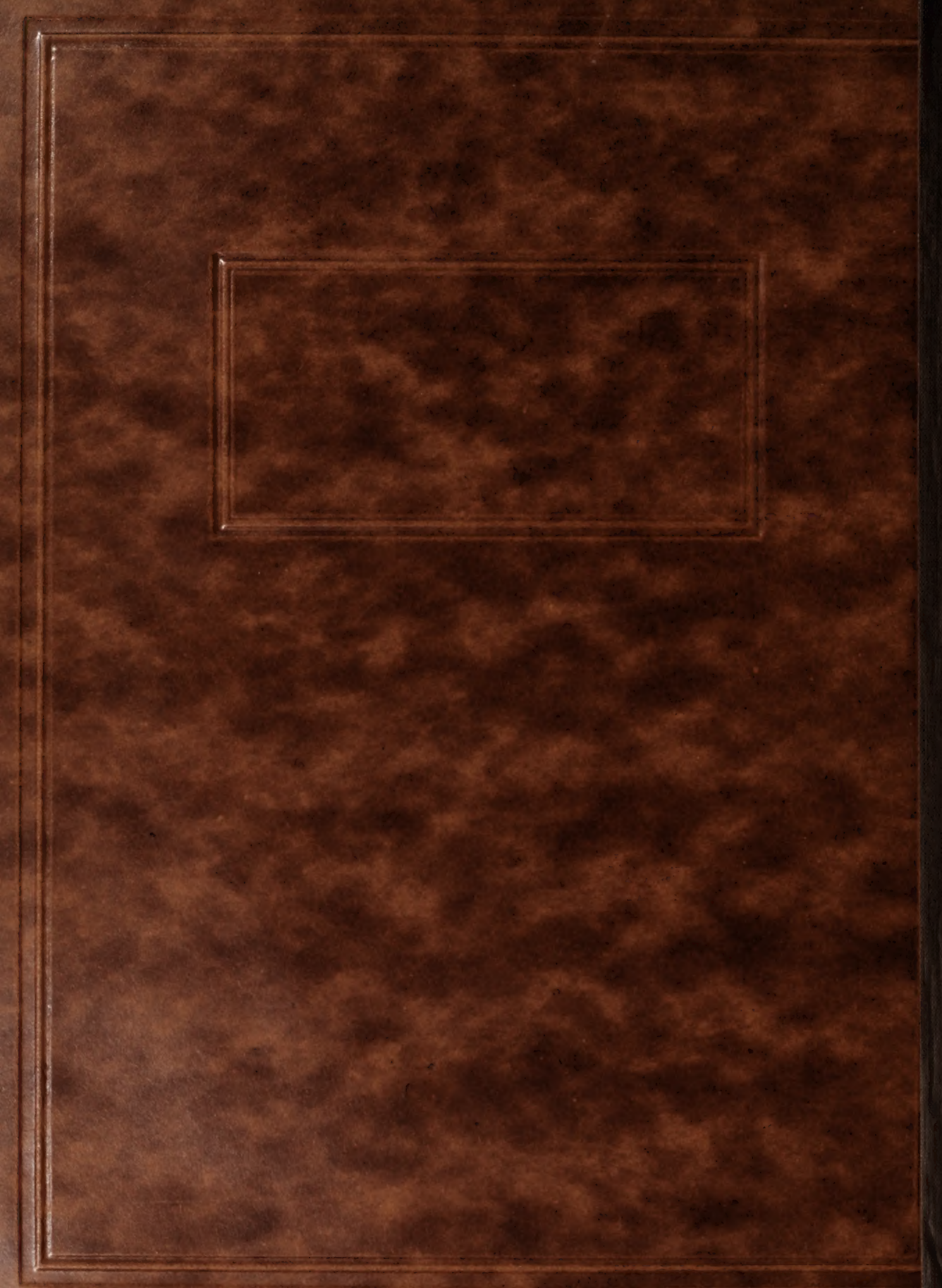


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BOSTON UNIVERSITY

GRADUATE SCHOOL

Thesis

THE ROLE OF VISCERAL AFFERENT NERVES

IN CARDIAC ARRHYTHMIAS

by

Frank L. Pettinga

(A.B., Calvin College, 1947)

submitted in partial fulfillment of the

requirements for the degree of

Master of Arts

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Historical Background

The cardiac status of a patient is one of the prime

Introduction

It is the purpose of this thesis to record the observations made and the conclusions drawn in investigating the mechanism of production of cardiac arrhythmias during cyclopropane anesthesia.

Cats were used as experimental animals. The effects of cyclopropane on the cardiac automatic centers were studied by means of an electrocardiograph before and after certain operative procedures.

That the anesthetic agents chloroform and cyclopropane lower the irritability threshold or excite the automatic tissues of the heart has been demonstrated both clinically and in the experimental laboratory. Levy and Lewis (12) first showed by means of electrocardiograms that chloroform anesthesia may produce a series of irregularities from automatic centers in the ventricles, ranging all the way from isolated extrasystoles to ventricular fibrillation. In 1926 Stewart, West, Kownatske and Jules (13) reported the occurrence of ventricular disturbances in dogs during experimental cyclopropane anesthesia. If circulatory embarrassment occurred

Historical Background

The cardiac status of a patient is one of the prime interests of the anesthetist. Whenever a new anesthetic agent is introduced, the anesthetist considers it imperative to know its action on the heart. In terms of function, such an agent may influence contractility, conductivity, irritability or automaticity. Irritability is a characteristic not only of contractile but also automatic tissue. Whenever there is a change in rate or a migration of the seat of impulse formation, it may be safely assumed that there have been changes in irritability of the automatic tissues either in line of depression, excitation, or both.

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during clinical anesthesia and pressor agents administered to alleviate the condition, it was observed that certain of these agents greatly augmented the irritability of the heart. In dogs this procedure often resulted in ventricular tachycardia, fibrillation and death (16).

These findings gave rise to experimental work which has branched into three phases. First, experiments were made to determine which pressor agents possessed these properties and which agents could be used safely. In addition to the practical value of these experiments it was hoped that by using a series of such drugs, some information might be obtained regarding the active groups in their molecules. A second phase of the problem consisted of investigating the agents and procedures that could be used to protect against the tachycardia resulting from the use of cardiac irritating drugs during chloroform and cyclopropane anesthesia. Also investigations have been carried out to determine the mechanisms involved in this phenomenon.

In this paper a brief review will be made of the work done thus far in each phase of this problem. Also a detailed account will be given of the work done in this laboratory in investigating the sites of action of cyclopropane and the irritating pressor agents in eliciting this phenomenon.

It was pointed out by Levy (13, 14, 15) that during chloroform anesthesia the injection of epinephrine might induce ventricular fibrillation. Meek and co-workers (16) demonstrated the production of ventricular tachycardia in dogs under cyclopropane anesthesia with the injection of a standard dose of epinephrine (0.01 mg./Kg.) and ventricular fibrillation in one out of five dogs with this dose. In a search for a safe pressor agent, twenty six sympathomimetic amines were tested (21, 22). Using comparable pressor doses it was found that all primary and secondary amines with a catechol nucleus gave ventricular tachycardia when injected during cyclopropane anesthesia. Some of these amines are β -(3,4-dihydroxy phenyl) β -hydroxy ethyl methyl amine (epinephrine), β -(3,4-dihydroxy phenyl) β -hydroxy isopropyl amine (cobefrin), β -(3,4-dihydroxy phenyl) ethyl methyl amine (epinine), β -(3,4-dihydroxy phenyl) β -hydroxy ethyl amine (arterenol), and several ketones. The common grouping of these agents is the catechol nucleus on the beta carbon atom -- a phenyl ring with hydroxyl groups in the 3,4 position. However, catechol itself was ineffective. Amines with one hydroxyl group on the phenyl ring such as β -(4 hydroxy phenyl) isopropyl amine (paredrine) gave only a sino-auriculo tachycardia. Also those agents with no

hydroxyl groups on the ring gave only an δ -A tachycardia with little evidence of ventricular irritation. These included β -phenyl isopropyl amine (amphetamine), β -phenyl β -hydroxy isopropyl methyl amine (ephedrine), β -phenyl β -hydroxy isopropyl amine (propadrine). Phenyl ephrine (Neosynephrine) was the only amine of the series which was without irritating properties. In nearly every trial of this pressor agent there was only a decrease in heart rate. At no time were A-V nodal rhythms, ventricular rhythms or tachycardias of any kind observed. For this reason β -(3-hydroxy phenyl) β -hydroxy ethyl methyl amine (phenyl ephrine, neo-synephrine) was felt to be the pressor agent of choice during cyclopropane anesthesia.

In 1936 Kurtz, Benet, and Shapiro (11) reported that about ten percent of patients under cyclopropane anesthesia show spontaneous multiple focus ventricular tachycardia. It was of clinical importance to protect against these arrhythmias. The clinical impression was that the dangerous period of anesthesia was early and that if the patients were carried safely through the first hour there was considerably less chance of initiating cardiac arrhythmias. This was later borne out experimentally (26), the conclusion being that as anesthesia progresses, cyclopropane has a so-called adrenolytic effect on the cardiovascular system.

In order that cyclopropane might be used safely through this period, methods for protecting against the irregularities were investigated. As will be shown, the conditions necessary for the production of cyclopropane-epinephrine tachycardia in the normal dog are that cyclopropane must be circulating, epinephrine must reach the heart, the sympathetic system and a brain center above the pons must be intact. This knowledge led to the trial of agents whose actions were thought to be divisible into four categories: drugs that depress the myocardium; adrenolytic drugs which block the response of the effector cells to epinephrine; sympathicolytic drugs which block the response to sympathetic nerve stimulation as well as the response of effector organs to epinephrine; and drugs which produce a functional decerebration (4). Some of the effective drugs are the myocardial depressants quinidine and procaine, the sympathicolytic agents F883 (diethyl-amino-methyl-benzyl-diozane), ergotamine, dibenamine (18, 19) and the adrenolytic agent yohimbine. Burstein (8, 9) has reported that intracardiac or intravenous injections of procaine during ventricular fibrillation reversed the rhythm to normal. However, in a large series by Stutzman and others (28) it was demonstrated that if the cardiac arrhythmias had progressed from ventricular flutter into true ventricular fibrillation, procaine was totally

ineffective in reversing the rhythm.

Since tetra ethyl ammonium ion is an effective autonomic ganglion blocking agent (1) it was considered likely that it might prove useful in blocking the cyclopropane-epinephrine response. It has been shown however that tetra ethyl ammonium chloride does not prevent the arrhythmias but augments them. The probable mechanism is a direct irritating effect on the heart (30).

Quite by accident it was noted that irregularities could not be produced after switching from ether to cyclopropane anesthesia (27). Also if a small amount of ether was mixed with a cyclopropane-oxygen mixture, complete protection from arrhythmias resulted.

Although the practical value lay in methods of protection against the cyclopropane-epinephrine phenomenon and in finding non irritating pressor agents, the problem of the actual mechanism of this response held most of the physiological interest.

The cyclopropane-epinephrine irregularities appeared very similar to the previously reported chloroform-epinephrine response. Levy (12) had shown in the cat that chloroform sensitizes the heart to stimulation of various kinds so that ventricular tachycardia and fibrillation may result. Beatie, Brown and Long (7) confirmed this work and also demonstrated that a center in the hypothalamus must be intact for the

production of extrasystoles of chloroform origin. Fibres pass from this region into the intermedio - lateral column of the grey matter of the cord from which come preganglionic sympathetic fibres which synapse in the stellate and upper thoracic white chain ganglia. From these ganglia post-ganglionic fibres run to the heart.

It was thought likely that this pathway was also essential for the production of cyclopropane epinephrine arrhythmias. Allen, Stutzman and Meek (3) found that decerebration or cardiac sympathectomy completely prevented the production of these arrhythmias in dogs. Vagotomy did not affect the mechanism. The site of action of epinephrine was found to be directly on the heart. However, the site of action of cyclopropane was not immediately determined.

To determine whether the receptor cells were in the hypothalamus, crossed circulations were established so that it was possible to expose only the cerebral circulation to cyclopropane (29). By this method it was shown that the cardiac arrhythmias were not obtained when cyclopropane was restricted to the brain, yet the arrhythmias were produced when cyclopropane reached the rest of the body but not the brain. And in this case anemic decerebration was effective in abolishing the irregularities.

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These observations pointed to a reflex sensitization of the heart, the efferent limb of the arc being from the hypothalamus, by way of the cardiac sympathetics. In localizing the afferent limb, it was found that either supradiaphragmatic or subdiaphragmatic splanchnicectomy prevented the arrhythmias in dogs. In some dogs stripping the nerves at the base of the superior mesenteric artery was effective. If cyclopropane was excluded from the gut by occluding visceral circulation, injected epinephrine caused no ventricular tachycardia. However, if cyclopropane again reached the gut by renewing circulation before irreversible degenerative changes had begun, the injection of epinephrine again produced ventricular tachycardia. The removal of the gastrointestinal tract from pylorus to rectum with accompanying mesentery abolished the arrhythmias. If, however, the gut were removed and the peripheral three centimeters of the mesentery with its circulation remained intact, the heart was reflexly irritated with the production of ventricular tachycardia after the injection of epinephrine.

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tensive action of epinephrine also protected the heart from chloroform-epinephrine arrhythmias. (25) It has recently been reported that dibenamine is effective in preventing cyclopropane-epinephrine arrhythmias (18, 19). However, a number of experiments have shown that the protective action of the adrenolytic compounds is not dependent on their pressure reversing properties, and that the cyclopropane-epinephrine ventricular rhythms are not due to a sudden rise in arterial pressure.

1. Certain amines that do not have a catechol ring in their structure produce a rise equal to that of epinephrine but elicit no cardiac abnormalities.

2. If a dog is subjected to a splanchnicectomy, the standard dose of epinephrine will produce a pressure rise equal to that in the normal dog but the cardiac rhythm will remain unchanged.

3. Using dibenamine, a small dose that will not reverse the pressure rise of epinephrine will protect the heart from ventricular rhythm (1).

4. After the pressure reversing effects of a larger dose of dibenamine have worn off, the heart is still protected (20). Thus it is evident from these four facts that the sensitization of the heart is not due to the sudden rise in

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arterial pressure. The production of ventricular tachycardia is more likely related to the chemical constitution of sympathomimetic amines.

Allen and others (5) reported that unpremedicated cats develop spontaneous ventricular arrhythmias when anesthetized with cyclopropane. In most cats the abnormal rhythms would come in bursts, with the sinus taking over between the periods of ventricular rhythm. That there was much individual variation was shown by the fact that both the intensity and duration of the arrhythmias were far from constant. The cat showing no arrhythmias was the exception however, since only one cat out of forty three maintained a normal rhythm during thirty minutes of anesthesia with 30% cyclopropane. Injected epinephrine in doses of 0.01 mg./Kg. somewhat increased the irregularities but in contrast to the reactions of dogs, doses of epinephrine up to 0.05 mg./Kg. in cats never resulted in fibrillation. In comparing these results it appeared that cats are more sensitive to cyclopropane than dogs since cats showed spontaneous arrhythmias. On the other hand the response of the heart to injected epinephrine was less than that of the dog. Thus the response of the cat is more similar to that of patients who show spontaneous irregularities in any plane of cyclopropane anesthesia. Patients

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do not appear to be as sensitive as cats however, the incidence being less than 10% (11, 31).

It was later shown (6) that vagotomy has no effect on the irregularities in cats, but cardiac sympathectomy immediately abolished the arrhythmias. This work gave rise to the present experiments which were performed to investigate the mechanism of genesis of cyclopropane arrhythmias in cats.

Methods

Anesthesia was induced in thirty four normal unpremedicated cats with a mixture of cyclopropane and oxygen. An endotracheal tube was inserted and connected through a soda lime carbon dioxide absorber to a hundred liter reservoir containing a mixture of thirty per cent cyclopropane in oxygen. A record of cardiac rhythm was obtained with an electrocardiograph (Lead II). The beam was under constant observation with records being taken every two minutes and when a change of rhythm was observed.

Control experiments were made on all the cats used and consisted of recording the cardiac response during thirty minutes of cyclopropane anesthesia. The abnormal rhythms occurred within a few minutes after induction and consisted

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of ventricular extrasystoles, bigeminal or trigeminal rhythm, and ventricular tachycardia. As was previously shown by Allen and others (5), these arrhythmias lasted from five to thirty minutes. Only those cats with long runs of abnormal rhythms were used in later experiments.

On a subsequent day the animals were again placed on a thirty per cent cyclopropane in oxygen mixture. As soon as a record of the abnormalities was obtained partial abdominal evisceration, partial abdominal denervation or bilateral adrenalectomy was performed. Partial abdominal evisceration consisted of removing the spleen, gastro-intestinal tract and accompanying mesentery from cardia to rectum. Visceral arteries were ligated within two centimeters from the aorta. Partial abdominal denervation consisted of removing the nerves at the base of the celiac and superior mesenteric arteries. Also that portion of the plexus and semilunar ganglion between these vessels and the aorta was removed. Functional bilateral adrenalectomy was performed by ligating the adrenal vessels. All procedures were completed within a period less than the control run of arrhythmias. The cardiac rhythm was recorded for at least ten minutes after completion of the surgical procedures.

In a number of animals the viscera were subjected to severe traumatic insults before completing the outlined operations. This did not abolish the arrhythmias and thus ruled out non-specific trauma as the cause of reversion to normal rhythm.

Results

Each of the surgical procedures as outlined above was performed on a series of cats. Partial abdominal evisceration in the first group abruptly abolished the preexisting ventricular tachycardia in five of seven cats. Bilateral adrenalectomy caused reversion in one of the remaining two and bilateral sympathectomy by sectioning the chain at level T-10 in the other¹. A second series was subjected to partial abdominal denervations. This abruptly abolished the arrhythmias in seven out of ten cats. One of the three unprotected cats had a reversion to a sinus rhythm with occasional extrasystoles. These in turn were abolished by bilateral sympathetic chain section at T-10.

¹ Chart I.

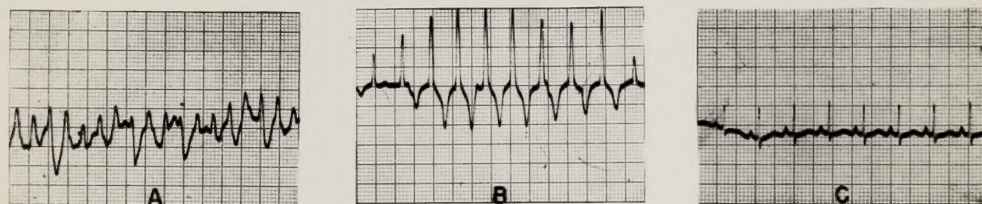
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I Chart I.

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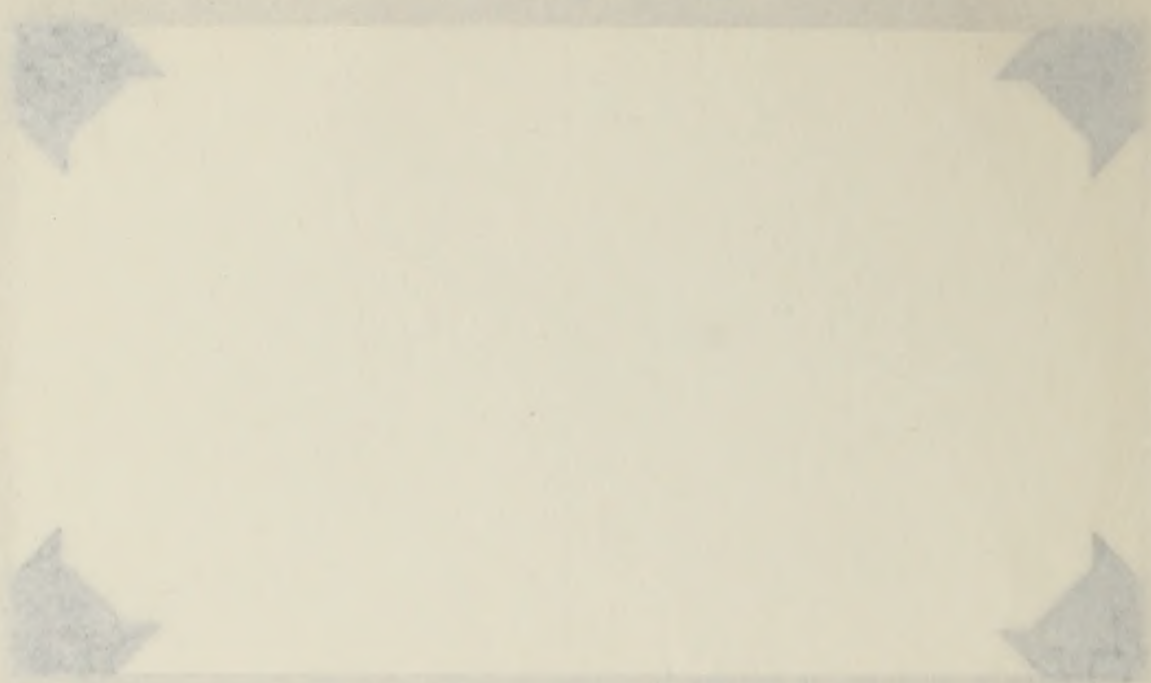


Representative EKG's of cat 3 under 30% cyclopropane anesthesia showing the effect of partial abdominal evisceration on the cardiac rhythm.

- A. Control period
- B. Immediately before the procedure
- C. After the procedure

* The writer wishes to express his appreciation to Mr. J. L. Jenks of the Sanborn Co. for supplying the Viso-Cardiette used in these studies.

Illustration I.*



Representative EKG's of cat 3 under 30% cyclopropane
anesthesia showing the effect of partial abdominal
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A. Control period

B. Immediately before the procedure

C. After the procedure

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KEY FOR CHARTS *

VT - Ventricular tachycardia (rate more than 250 per minute).

V&PC - ventricular rhythm with occasional supraventricular beats.

Bigem - bigeminal rhythm (SA - V).

MPC - many ventricular premature contractions (more than one ventricular beat to four supraventricular beats.)

FPC - few ventricular premature contractions.

FAVPC - few auricular-ventricular premature contractions.

AV - auriculo-ventricular rhythm

SA - Sinoauricular rhythm

* These abbreviations are used in charts I, II and III.

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FPC - few ventricular premature contractions.

F&VPC - few supraventricular-ventricular premature contractions.

AV - atrio-ventricular rhythm

SA - Sinus bradycardia rhythm

* These abbreviations are used in charts I, II and III.

CHART I

CARDIAC RHYTHM IN CATS ANESTHETIZED WITH CYCLOPROPANE

| CONTROL RUN OF ARRHYTHMIAS | | | | | PARTIAL ABDOMINAL EVISCERATION | | ADDITIONAL PROCEDURES THAT REESTABLISHED NORMAL RHYTHM |
|-------------------------------|-----------------|------|-----|-----|-----------------------------------|--------------|--|
| Cat No. | VT | V&PC | MPC | FPC | RHYTHM BEFORE | RHYTHM AFTER | |
| | Time in Minutes | | | | | | |
| 1 | 3 | 6 | 16 | | AV&MVPC | SA | Bilateral adrenalectomy |
| 2 | | 4 | 20 | | VT | Bigem | |
| 3 | 10 | | | | VT | AV | |
| 4 | | 15 | | 2 | Bigem | Bigem | Sympathetic chains sectioned at T-10 |
| 5 | 12 | | 10 | 8 | V&FAVPC | AV | |
| 6 | | | | | V&FAVPC | SA | |
| 7 | | | | | V&FAVPC | SA | |

Of the remaining two the sino-auriculo node became the pacemaker in one of the cats after sectioning the preaortic sympathetic nerves going to the inferior mesenteric plexus. Bilateral cardiac sympathectomy protected the other². After a run of ventricular tachycardia had been recorded in a third series, bilateral adrenalectomies were performed. This reverted the rhythm back to normal within two minutes in 15 out of 17 cats. In one of the unprotected cats the sinus node regained control after partial abdominal evisceration and in the other after bilateral section of the sympathetic chain at level T-10³.

In order to determine the role of epinephrine in cyclopropane induced arrhythmias in the cat, a small dose of epinephrine, 0.0025-0.01 mg./Kg. was given to cats 29 through 34, which had been protected from cardiac arrhythmias by bilateral adrenalectomies. The minimal dose for each cat produced a ventricular rhythm which lasted about 50 seconds. Subsequent partial abdominal denervation then protected these cats from an equal dose of epinephrine.

Discussion

That these procedures were responsible for the abolition of the preexisting ventricular tachycardia cannot be definitely

2 Chart II.

3 Chart III.

Of the remaining two the sino-aortic node became the
pacemaker in one of the cases after sectioning the ganglion
sympathetic nerves going to the inferior mesenteric ganglion.
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a run of ventricular tachycardia had been recorded in a
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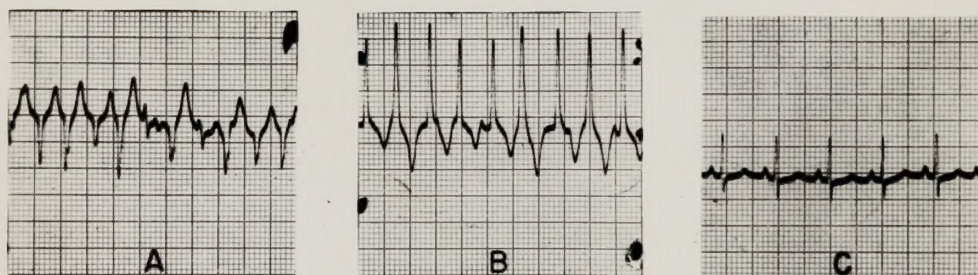
In order to determine the role of sympathetic innervation in
producing induced arrhythmias in the cat, a series of
experiments were performed. The vagus nerves were cut
through the thorax and then isolated from outside the
cage by bilateral pneumothoraces. The animal was then
each one produced a ventricular rhythm which lasted 10-20
30 seconds. Subsequently further isolation of sympathetic
projected these cats from an animal room of observation.

Discussion

That these experiments were responsible for the abolition
of the normal sino-aortic node rhythm cannot be doubted.

2. Gantt II.
3. Gantt III.

Illustration II.



Representative EKG's of cat 12 under 30% cyclopropane anesthesia showing the effect of partial abdominal denervation on the cardiac rhythm.

- A. Control period
- B. Immediately before procedure
- C. After procedure

Illustration II.

Representative EKG's of cat 12 under 50% cyclopropane anesthesia showing the effect of partial abdominal denervation on the cardiac rhythm.

- A. Control period
- B. Immediately before procedure
- C. After procedure

ELIGENCIA BOND

CHART II

CARDIAC RHYTHM IN CATS ANESTHETIZED WITH CYCLOPROPANE

| CONTROL RUN OF ARRHYTHMIAS | | | | | PARTIAL ABDOMINAL DENERVATION | | ADDITIONAL PROCEDURES THAT REESTABLISHED NORMAL RHYTHM |
|-------------------------------|-----------------|-------|------|-----|----------------------------------|--------------|---|
| Cat No. | VT V | Bigem | V&PC | MPC | Rhythm Before | Rhythm After | |
| | Time in Minutes | | | | | | |
| 8 | | | | 12 | VT | SA | |
| 9 | 4 | 4 | | 16 | VT | SA | |
| 10 | 18 | | 10 | | V&FVPC | SA | |
| 11 | 12 | | | 4 | VT | SA | |
| 12 | 20 | | | 7 | VT | SA | |
| 13 | 5 | | | | VT | SA | |
| 14 | 30 | | | | VT | V | Preaortic nerves sectioned |
| 15 | 16 | | 11 | | VT | SA | |
| 16 | 5 | | 25 | | VT | SA&FVPC | Sympathetic chains sectioned at T-10 |
| 17 | 30 | | | | VT | V | Sympathetic chains sectioned at T-10; cardiac sympathect- omy |

TABLE II

CHANGING RELATION IN CATTLE VACCINATION WITH CYCLOSPOROSES

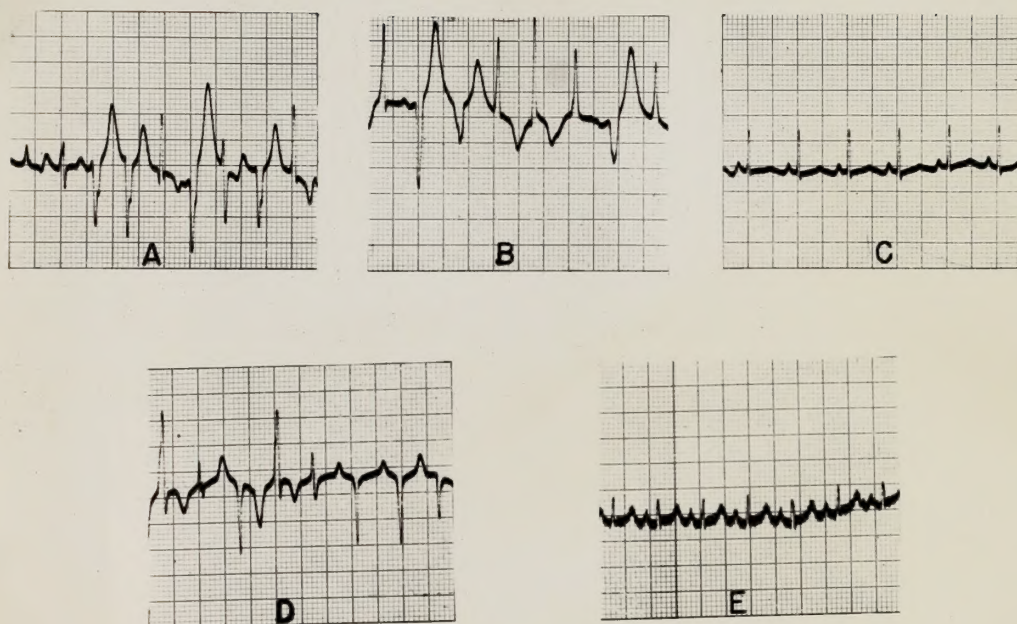
| GENERAL INFORMATION | | VACCINATION | | CYCLOSPOROSIS | | RELATION | | RELATION | |
|---------------------|-----|-------------|-----|---------------|-----|----------|-----|----------|-----|
| DATE | NO. | DATE | NO. | DATE | NO. | DATE | NO. | DATE | NO. |
| 1910 | 1 | 1910 | 1 | 1910 | 1 | 1910 | 1 | 1910 | 1 |
| 1911 | 2 | 1911 | 2 | 1911 | 2 | 1911 | 2 | 1911 | 2 |
| 1912 | 3 | 1912 | 3 | 1912 | 3 | 1912 | 3 | 1912 | 3 |
| 1913 | 4 | 1913 | 4 | 1913 | 4 | 1913 | 4 | 1913 | 4 |
| 1914 | 5 | 1914 | 5 | 1914 | 5 | 1914 | 5 | 1914 | 5 |
| 1915 | 6 | 1915 | 6 | 1915 | 6 | 1915 | 6 | 1915 | 6 |
| 1916 | 7 | 1916 | 7 | 1916 | 7 | 1916 | 7 | 1916 | 7 |
| 1917 | 8 | 1917 | 8 | 1917 | 8 | 1917 | 8 | 1917 | 8 |
| 1918 | 9 | 1918 | 9 | 1918 | 9 | 1918 | 9 | 1918 | 9 |
| 1919 | 10 | 1919 | 10 | 1919 | 10 | 1919 | 10 | 1919 | 10 |
| 1920 | 11 | 1920 | 11 | 1920 | 11 | 1920 | 11 | 1920 | 11 |
| 1921 | 12 | 1921 | 12 | 1921 | 12 | 1921 | 12 | 1921 | 12 |
| 1922 | 13 | 1922 | 13 | 1922 | 13 | 1922 | 13 | 1922 | 13 |
| 1923 | 14 | 1923 | 14 | 1923 | 14 | 1923 | 14 | 1923 | 14 |
| 1924 | 15 | 1924 | 15 | 1924 | 15 | 1924 | 15 | 1924 | 15 |
| 1925 | 16 | 1925 | 16 | 1925 | 16 | 1925 | 16 | 1925 | 16 |
| 1926 | 17 | 1926 | 17 | 1926 | 17 | 1926 | 17 | 1926 | 17 |
| 1927 | 18 | 1927 | 18 | 1927 | 18 | 1927 | 18 | 1927 | 18 |
| 1928 | 19 | 1928 | 19 | 1928 | 19 | 1928 | 19 | 1928 | 19 |
| 1929 | 20 | 1929 | 20 | 1929 | 20 | 1929 | 20 | 1929 | 20 |
| 1930 | 21 | 1930 | 21 | 1930 | 21 | 1930 | 21 | 1930 | 21 |
| 1931 | 22 | 1931 | 22 | 1931 | 22 | 1931 | 22 | 1931 | 22 |
| 1932 | 23 | 1932 | 23 | 1932 | 23 | 1932 | 23 | 1932 | 23 |
| 1933 | 24 | 1933 | 24 | 1933 | 24 | 1933 | 24 | 1933 | 24 |
| 1934 | 25 | 1934 | 25 | 1934 | 25 | 1934 | 25 | 1934 | 25 |
| 1935 | 26 | 1935 | 26 | 1935 | 26 | 1935 | 26 | 1935 | 26 |
| 1936 | 27 | 1936 | 27 | 1936 | 27 | 1936 | 27 | 1936 | 27 |
| 1937 | 28 | 1937 | 28 | 1937 | 28 | 1937 | 28 | 1937 | 28 |
| 1938 | 29 | 1938 | 29 | 1938 | 29 | 1938 | 29 | 1938 | 29 |
| 1939 | 30 | 1939 | 30 | 1939 | 30 | 1939 | 30 | 1939 | 30 |
| 1940 | 31 | 1940 | 31 | 1940 | 31 | 1940 | 31 | 1940 | 31 |
| 1941 | 32 | 1941 | 32 | 1941 | 32 | 1941 | 32 | 1941 | 32 |
| 1942 | 33 | 1942 | 33 | 1942 | 33 | 1942 | 33 | 1942 | 33 |
| 1943 | 34 | 1943 | 34 | 1943 | 34 | 1943 | 34 | 1943 | 34 |
| 1944 | 35 | 1944 | 35 | 1944 | 35 | 1944 | 35 | 1944 | 35 |
| 1945 | 36 | 1945 | 36 | 1945 | 36 | 1945 | 36 | 1945 | 36 |
| 1946 | 37 | 1946 | 37 | 1946 | 37 | 1946 | 37 | 1946 | 37 |
| 1947 | 38 | 1947 | 38 | 1947 | 38 | 1947 | 38 | 1947 | 38 |
| 1948 | 39 | 1948 | 39 | 1948 | 39 | 1948 | 39 | 1948 | 39 |
| 1949 | 40 | 1949 | 40 | 1949 | 40 | 1949 | 40 | 1949 | 40 |
| 1950 | 41 | 1950 | 41 | 1950 | 41 | 1950 | 41 | 1950 | 41 |
| 1951 | 42 | 1951 | 42 | 1951 | 42 | 1951 | 42 | 1951 | 42 |
| 1952 | 43 | 1952 | 43 | 1952 | 43 | 1952 | 43 | 1952 | 43 |
| 1953 | 44 | 1953 | 44 | 1953 | 44 | 1953 | 44 | 1953 | 44 |
| 1954 | 45 | 1954 | 45 | 1954 | 45 | 1954 | 45 | 1954 | 45 |
| 1955 | 46 | 1955 | 46 | 1955 | 46 | 1955 | 46 | 1955 | 46 |
| 1956 | 47 | 1956 | 47 | 1956 | 47 | 1956 | 47 | 1956 | 47 |
| 1957 | 48 | 1957 | 48 | 1957 | 48 | 1957 | 48 | 1957 | 48 |
| 1958 | 49 | 1958 | 49 | 1958 | 49 | 1958 | 49 | 1958 | 49 |
| 1959 | 50 | 1959 | 50 | 1959 | 50 | 1959 | 50 | 1959 | 50 |
| 1960 | 51 | 1960 | 51 | 1960 | 51 | 1960 | 51 | 1960 | 51 |
| 1961 | 52 | 1961 | 52 | 1961 | 52 | 1961 | 52 | 1961 | 52 |
| 1962 | 53 | 1962 | 53 | 1962 | 53 | 1962 | 53 | 1962 | 53 |
| 1963 | 54 | 1963 | 54 | 1963 | 54 | 1963 | 54 | 1963 | 54 |
| 1964 | 55 | 1964 | 55 | 1964 | 55 | 1964 | 55 | 1964 | 55 |
| 1965 | 56 | 1965 | 56 | 1965 | 56 | 1965 | 56 | 1965 | 56 |
| 1966 | 57 | 1966 | 57 | 1966 | 57 | 1966 | 57 | 1966 | 57 |
| 1967 | 58 | 1967 | 58 | 1967 | 58 | 1967 | 58 | 1967 | 58 |
| 1968 | 59 | 1968 | 59 | 1968 | 59 | 1968 | 59 | 1968 | 59 |
| 1969 | 60 | 1969 | 60 | 1969 | 60 | 1969 | 60 | 1969 | 60 |
| 1970 | 61 | 1970 | 61 | 1970 | 61 | 1970 | 61 | 1970 | 61 |
| 1971 | 62 | 1971 | 62 | 1971 | 62 | 1971 | 62 | 1971 | 62 |
| 1972 | 63 | 1972 | 63 | 1972 | 63 | 1972 | 63 | 1972 | 63 |
| 1973 | 64 | 1973 | 64 | 1973 | 64 | 1973 | 64 | 1973 | 64 |
| 1974 | 65 | 1974 | 65 | 1974 | 65 | 1974 | 65 | 1974 | 65 |
| 1975 | 66 | 1975 | 66 | 1975 | 66 | 1975 | 66 | 1975 | 66 |
| 1976 | 67 | 1976 | 67 | 1976 | 67 | 1976 | 67 | 1976 | 67 |
| 1977 | 68 | 1977 | 68 | 1977 | 68 | 1977 | 68 | 1977 | 68 |
| 1978 | 69 | 1978 | 69 | 1978 | 69 | 1978 | 69 | 1978 | 69 |
| 1979 | 70 | 1979 | 70 | 1979 | 70 | 1979 | 70 | 1979 | 70 |
| 1980 | 71 | 1980 | 71 | 1980 | 71 | 1980 | 71 | 1980 | 71 |
| 1981 | 72 | 1981 | 72 | 1981 | 72 | 1981 | 72 | 1981 | 72 |
| 1982 | 73 | 1982 | 73 | 1982 | 73 | 1982 | 73 | 1982 | 73 |
| 1983 | 74 | 1983 | 74 | 1983 | 74 | 1983 | 74 | 1983 | 74 |
| 1984 | 75 | 1984 | 75 | 1984 | 75 | 1984 | 75 | 1984 | 75 |
| 1985 | 76 | 1985 | 76 | 1985 | 76 | 1985 | 76 | 1985 | 76 |
| 1986 | 77 | 1986 | 77 | 1986 | 77 | 1986 | 77 | 1986 | 77 |
| 1987 | 78 | 1987 | 78 | 1987 | 78 | 1987 | 78 | 1987 | 78 |
| 1988 | 79 | 1988 | 79 | 1988 | 79 | 1988 | 79 | 1988 | 79 |
| 1989 | 80 | 1989 | 80 | 1989 | 80 | 1989 | 80 | 1989 | 80 |
| 1990 | 81 | 1990 | 81 | 1990 | 81 | 1990 | 81 | 1990 | 81 |
| 1991 | 82 | 1991 | 82 | 1991 | 82 | 1991 | 82 | 1991 | 82 |
| 1992 | 83 | 1992 | 83 | 1992 | 83 | 1992 | 83 | 1992 | 83 |
| 1993 | 84 | 1993 | 84 | 1993 | 84 | 1993 | 84 | 1993 | 84 |
| 1994 | 85 | 1994 | 85 | 1994 | 85 | 1994 | 85 | 1994 | 85 |
| 1995 | 86 | 1995 | 86 | 1995 | 86 | 1995 | 86 | 1995 | 86 |
| 1996 | 87 | 1996 | 87 | 1996 | 87 | 1996 | 87 | 1996 | 87 |
| 1997 | 88 | 1997 | 88 | 1997 | 88 | 1997 | 88 | 1997 | 88 |
| 1998 | 89 | 1998 | 89 | 1998 | 89 | 1998 | 89 | 1998 | 89 |
| 1999 | 90 | 1999 | 90 | 1999 | 90 | 1999 | 90 | 1999 | 90 |
| 2000 | 91 | 2000 | 91 | 2000 | 91 | 2000 | 91 | 2000 | 91 |
| 2001 | 92 | 2001 | 92 | 2001 | 92 | 2001 | 92 | 2001 | 92 |
| 2002 | 93 | 2002 | 93 | 2002 | 93 | 2002 | 93 | 2002 | 93 |
| 2003 | 94 | 2003 | 94 | 2003 | 94 | 2003 | 94 | 2003 | 94 |
| 2004 | 95 | 2004 | 95 | 2004 | 95 | 2004 | 95 | 2004 | 95 |
| 2005 | 96 | 2005 | 96 | 2005 | 96 | 2005 | 96 | 2005 | 96 |
| 2006 | 97 | 2006 | 97 | 2006 | 97 | 2006 | 97 | 2006 | 97 |
| 2007 | 98 | 2007 | 98 | 2007 | 98 | 2007 | 98 | 2007 | 98 |
| 2008 | 99 | 2008 | 99 | 2008 | 99 | 2008 | 99 | 2008 | 99 |
| 2009 | 100 | 2009 | 100 | 2009 | 100 | 2009 | 100 | 2009 | 100 |

RELATION BETWEEN CYCLOSPOROSES AND VACCINATION

RELATION BETWEEN CYCLOSPOROSES AND VACCINATION

RELATION BETWEEN CYCLOSPOROSES AND VACCINATION

Illustration III.



Representative EKG's of cat 32 under 30% cyclopropane anesthesia showing the effect of bilateral adrenalectomy on the cardiac rhythm.

- A. Control period
- B. Immediately before procedure
- C. After procedure
- D. The effect of a small dose of IV epinephrine after bilateral adrenalectomy
- E. The effect of the same dose of epinephrine after bilateral adrenalectomy and partial abdominal denervation.

Illustration III.

Representative EKG's of cat 32 under 30% cyclopropane anesthesia showing the effect of bilateral adrenalectomy on the cardiac rhythm.

- A. Control period
- B. Immediately before procedure
- C. After procedure
- D. The effect of a small dose of IV epinephrine after bilateral adrenalectomy
- E. The effect of the same dose of epinephrine after bilateral adrenalectomy and partial abdominal denervation.

CHART III

CARDIAC RHYTHM IN CATS ANESTHETIZED WITH CYCLOPROPANE

CONTROL RUN OF
ARRHYTHMIAS

BILATERAL ADRENALECTOMY

ADDITIONAL PROCEDURES
THAT REESTABLISHED
NORMAL RHYTHM

| Cat No. | VT | Bigem | V&PC | MPC | FPC | Rhythm Before | Rhythm After | ADDITIONAL PROCEDURES THAT REESTABLISHED NORMAL RHYTHM |
|---------|----|-----------------|------|-----|-----|---------------|--------------|--|
| 18 | 20 | Time in Minutes | | 5 | | VT | SA | |
| 19 | | 9 | | | | V&FAVPC | AV | |
| 20 | | | 10 | | | VT | SA | |
| 21 | | | 12 | 12 | | VT | SA | |
| 22 | | | 15 | 15 | | VT | V&FAVPC | |
| 23 | | | 23 | | | V&FAVPC | V&FAVPC | Partial abdominal denervation |
| 24 | 23 | 2 | | 3 | | VT | SA | |
| 25 | 7 | | | 9 | 6 | VT | SA | |
| 26 | 8 | | | 7 | | VT | SA | |
| 27 | 30 | | | | | VT | VT | Sympathetic chains sectioned at T-10 |
| 28 | 30 | | | | | VT | SA | |

CHART III (CONTINUED)

| Cat No. | CONTROL RUN OF ARRHYTHMIAS | | | | | BILATERAL ADRENALECTOMY | | ADDITIONAL PROCEDURES THAT REESTABLISHED NORMAL RHYTHM | |
|---------|----------------------------|-----------------|------|-----|-----|-------------------------|--------------|--|--|
| | VT | Bigem | V&PC | MPC | FPC | Rhythm Before | Rhythm After | | |
| | | TIME IN MINUTES | | | | | | | |
| 28 | 30 | | | | | VT | SA | | |
| 29 | 30 | | | | | VT | SA | | |
| 30 | 1 | | 5.5 | 19 | 15 | VT | SA | | |
| 31 | 12 | 2 | | | | VT | SA | | |
| 32 | 20 | 1 | | 5 | 4 | VT | SA | | |
| 33 | 15 | | | 1 | 1 | VT | SA | | |
| 34 | 28 | | | | | VT | SA | | |

demonstrated. The possibility that the adrenolytic action of cyclopropane was responsible for the reversion should not be overlooked. It must be remembered, however, that cyclopropane arrhythmias in cats are nearly reproducible from day to day if conditions are kept constant (5). Also the surgical procedures were finished within a period less than the control run of ventricular tachycardia. As each procedure was completed, the rhythm abruptly reverted to normal. In the case of the adrenalectomies the two minute interval between surgery and cessation of abnormal rhythms is approximately the time necessary for the disappearance of circulating epinephrine from the blood stream. From these observations it is statistically valid to conclude that abolition of the irregularities was due to the procedures and not to the adrenolytic action of cyclopropane.

Bronk (10) has indirectly shown that changes in blood pressure of the mesenteric circulation of the cat are not responsible for this phenomenon. By recording potentials from splanchnic nerves and nerves from Paccinian corpuscles in the mesentery, he found that varying the pressure caused an increase in frequency and amplitude of spike potentials. However, since there were no other observed changes in the status of the cat, no end effects could be shown to be caused by the increased potentials.

Conclusions

From the present results and those of Allen it is concluded that cyclopropane increases the irritability of the cat's heart reflexly. Afferent receptor cells which are possibly chemoreceptor in nature respond to circulating cyclopropane. The exact site of these cells has not been determined. It has been demonstrated, however, that the afferent impulses from the abdomen pass through the superior mesenteric and semilunar ganglia and are carried by fibres traveling with the splanchnic nerves. Efferent impulses pass by way of the superior cervical and stellate ganglia, along the cardiac sympathetics to the heart. Endogenous epinephrine is necessary for the occurrence of spontaneous ventricular arrhythmias under these conditions. The role of endogenous epinephrine must still be determined. The exact location of the afferent nerves and their endings in the gut and also the physiological role that this mechanism plays in the intact animal are under investigation.

The writer desires to express his appreciation to
Dr. J. W. Stutzman for his personal guidance and help in
the course of these experiments.

Abstract of the Thesis

It has been reported that dogs will show severe cardiac arrhythmias during cyclopropane anesthesia if injected with a small dose of epinephrine. Other pressor amines with a catechol nucleus have a similar effect. Sympathicolytic and adrenolytic drugs will prevent this response. Cyclopropane acts on receptors in the abdomen and reflexly increases the irritability of the heart.

The purpose of the present experiments was to determine the effect of evisceration, partial abdominal denervation or adrenalectomy on cyclopropane induced cardiac arrhythmias in the cat. After induction with a cyclopropane-oxygen mixture, unmedicated cats were intubated and maintained in deep surgical anesthesia by rebreathing a mixture of thirty per cent cyclopropane in oxygen from a 100 liter reservoir. The beam of the electrocardiograph (Lead II) was under constant observation. Records were taken every two minutes and when a change in rhythm was observed. Control experiments consisted of recording the cardiac response during thirty minutes of cyclopropane anesthesia. On a subsequent day the animals were again placed on the anesthetic mixture. As soon as a record of cardiac arrhythmias was obtained the surgery was performed.

The findings of Allen et al. (Anesthesiology 3:530,1942) was confirmed that without exogenous epinephrine cats develop cardiac arrhythmias during cyclopropane anesthesia. The arrhythmias consist of ventricular premature contractions, bigeminal rhythm, and ventricular tachycardia. Partial abdominal evisceration abruptly abolished the arrhythmias in 5 out of 7 cats. This procedure consisted of removing the spleen, gastrointestinal tract and accompanying mesentery from cardia to rectum. Visceral arteries were ligated within 2 cm of the aorta.

In another series 7 out of 10 cats were protected from the abnormal rhythms by partial abdominal denervation. The nerves along the celiac and superior mesenteric arteries were severed. Also the plexus and semilunar ganglion between these vessels and the abdominal aorta were removed.

Bilateral adrenalectomy caused the preexisting ventricular tachycardia to revert to S-A rhythm within two minutes in 15 of 17 cats. In the last series, 6 of the adrenalectomized cats were given intravenous injections of a small dose of epinephrine, 0.0025 - 0.01 mg./Kg. This produced a short run of ventricular tachycardia. Subsequent partial abdominal denervation protected these cats from the same dose of epinephrine.

It is concluded that the irritability threshold of the heart of the cat is lowered during cyclopropane anesthesia.

A reflex mechanism is responsible. Afferent impulses from the abdomen are carried by fibres traveling with the splanchnic nerves to a brain center. Efferent impulses pass along the cardiac sympathetics to the heart. Circulating endogenous epinephrine induces the abnormal rhythm in the sensitized heart.

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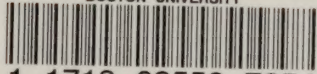
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